SUPPLEMENTAL MATERIAL

Methods:

Source population

All participants in the study were members of the Kaiser Permanente Medical Care Plan in Northern California (KPNC), an integrated health care delivery system that currently cares for over 4.1 million patients. Since 1995, KPNC has had comprehensive electronic health records (EHRs) that include detailed information on all aspects of medical care. The KPNC EHR system includes a customized set of EPIC applications implemented in 2006. A Research Database (RDB) aggregates data from the EPIC applications as well as from administrative and legacy clinical databases into a single data warehouse optimized for efficient research query and retrieval. The RDB was the source of data for the present analyses. Participants were selected from the Genetic Epidemiology Research on Adult Health and Aging (GERA) cohort (110,266 individuals), part of the KPNC Research Program on Genes, Environment, and Health (RPGEH). GERA is a research resource that links the EHRs of participants with health surveys and genome-wide single nucleotide polymorphism (SNP) data. Lipid panel measurements, dispensing records for prescriptions used to treat hyperlipidemia, and other medical records from 1996 to 2013 were extracted. Lipid panels always included total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), and high-density lipoprotein cholesterol (HDL-C) measurements. Only fasting lipid panels were used. LDL-C was calculated using the Friedewald equation [1] or measured directly (when TG>400). Hypertension was defined as having at least two hypertension ICD-9 codes on different dates. We determined diabetes status for each subject based on criteria from the Kaiser Diabetes Registry [2]. We defined smokers as current or former cigarette smokers. Race/ethnicity was based on self-report [3]. Participants gave informed

consent and the study was approved by the Kaiser Foundation Research Institute Institutional Review Board (IRB).

Study sample

We limited the current analysis to cohort participants who had at least two dispensing records of any statin (i.e. "statin user", Figure 1). This requirement was used to eliminate non-adherent participants (e.g., due to statin-intolerance), based on prior data that the first statin refill (i.e., the second total fill) is a strong predictor of adherence [4]. To reduce the likelihood of including participants who were not new users of statins, we also excluded participants whose initial statin prescription was within 6 months of entering KPNC membership (Figure 1). We also required that each participant have at least one lipid panel before and after the initial statin prescription. To qualify as a lipid panel used for data analysis, the panel could not have been obtained within the time frame of use of a non-statin dyslipidemia medication (from the day the non-statin medication was dispensed to three weeks following the end of the non-statin days' supply) to ensure that the response was not influenced by a therapy other than statin. In addition, we only included participants with lipid panels obtained in an outpatient setting. Non-statin lipid-modifying therapies included prescription fibrates, niacin, ezetimibe, anion-exchange resins, and prescription omega-3 fatty acids. To ensure adequate sample sizes for our stratified analyses, only participants of the major race/ethnicity groups (White/European, Hispanic/Latino, East Asian, or Black/African) who were initiated on the primarily used statin types (lovastatin, simvastatin, atorvastatin, or pravastatin) were included for analysis.

Statin lipid response

For each study participant, statin response was calculated using the most recent qualifying pretreatment lipid panel (immediately before statin initiation) and the earliest qualifying on-treatment lipid panel (immediately after statin initiation). To ensure that the lipid panel was reflective of response to the first statin prescription, a qualifying on-treatment lipid panel had to have been measured within a period that spanned from three weeks following the initial statin prescription record to three weeks beyond the days' supply of that prescription (Supplemental Figure 2). This time frame is based on evidence suggesting that LDL-C levels reach steady state within only a few weeks of beginning therapy [5]. Response was expressed as the percent change from pretreatment level, calculated as (Y-X)/X, where Y is the on-treatment value and X is the pretreatment value.

Deriving daily dose

We determined the impact of statin dosing on LDL-C response in an analysis that combined statin types. For each prescription dispensed, two sets of two variables each were available to independently define the tablets per day dispensed to each participant: (1) days' supply and total tablets supplied and (2) doses per day and tablets per dose. We excluded participants with initial statin prescriptions for which the two sets of variables calculated different numbers of tablets per day (Figure 1). We then multiplied tablets per day by strength (mg per tablet) to derive a prescribed daily dose (PDD) for each prescription. To account for differences in potency among statin types, we generated a defined daily dose (DDD) value for each type such that 1.0 DDD was equal to 40 mg of lovastatin daily and all of its equipotent counterparts (Supplemental Table 1). We determined relative potency among statin types using the Food and Drug Administration (FDA) statin LDL-C lowering dose equivalency table [6]. We anticipated that after adjusting for DDD, there would be no association between statin type and response (e.g., we anticipated that

lovastatin and atorvastatin would have the same response since lovastatin 40 mg and atorvastatin 10 mg were both given the same DDD value based on the dose equivalency table).

Statistical analyses

The relationship between DDD and statin LDL-C response was determined using univariate and multivariate linear regression. DDD was $\log_2$-transformed to determine the impact of doubling statin dose. Pre-specified covariates that could impact LDL-C response included age, race/ethnicity (reference group: White/European patients), sex, body mass index (BMI), statin type (reference group: lovastatin users), hypertension, diabetes, and smoking[7]. We also reran the primary analysis stratified by statin type, sex, and race/ethnicity in various combinations to determine LDL-C statin dose-response within these individual subgroups. Due to the low prevalence of potential drug-drug interactions in the population, we did not include use of interacting drugs as a covariate.

We determined the relationship between DDD and statin response of TG, HDL-C, and non-high-density lipoprotein cholesterol (non-HDL-C) similarly to the analysis of statin LDL-C response.

For the heritability analysis, we determined the correlations of the transformed residuals in the individual subsets of first-degree relatives (Pearson correlation for 229 parent-offspring pairs, intraclass correlation for 296 sibling pairs). To derive a heritability estimate, we analyzed the entire sample of 1,036 individuals who had at least one first-degree relative using a variance-components approach in SOLAR-Eclipse v8.1.1[8] Familial first-degree relationships were previously determined genetically using KING v1.4 [3].

All analyses were done in R v3.4.2[9], unless otherwise noted.

Supplemental Table 1: Statin dose low-density lipoprotein cholesterol (LDL-C) lowering equivalency chart for the generation of defined daily dose (DDD) values

DDD	Intensity*	Response†	Daily dose (mg)‡			
			Atorva	Lova	Prava	Simva
1/4	Low	20-26		10	10	5
1/2	Low	24-32		20	20	10
1	Moderate	30-39	10	40	40	20
2	Moderate	37-45	20	80	80	40
4	High	46-52	40			80
8	High	51-60	80			

*Intensity classification was derived from the 2013 American College of Cardiology (ACC)/ American Heart Association (AHA) cholesterol treatment guidelines [10]

†Response is shown as the range of point estimates for patients with primary hyperlipidemia or mixed dyslipidemia (mean percent LDL-C reduction from pretreatment level at 12 weeks) from dose-ranging studies in the Product Labeling of each statin type [11-14].

‡Daily dose equivalencies across type for each DDD value were derived from a modified version of the FDA "Relative LDL-lowering Efficacy of Statin and Statin-based Therapies" [6]

Atorva, atorvastatin; lova, lovastatin; prava, pravastatin; simva, simvastatin

Supplemental Table 2: Statin low-density lipoprotein cholesterol (LDL-C) dose-response by sex and race/ethnicity among lovastatin users

	1/8	1/4	1/2	1	2	Dose response
Male (N=10,059)	-17.4 (-18.2, -16.8)	-22.7 (-23.5, -22.0)	-28.3 (-29.0, -27.5)	-33.9 (-34.7, -33.1)	-39.4 (-40.2, -38.8)	β = -5.58, SE = 0.207 P = $5.1*10^{-155}$
Female (N=10,794)	-18.2 (-19.0, -17.5)	-23.9 (-24.7, -23.1)	-29.4 (-30.2, -28.6)	-35.0 (-35.8, -34.2)	-40.0 (-41.1, -39.5)	β = -6.04, SE = 0.194 P = $6.6*10^{-205}$
White/European (N=17,049)	-17.6 (-18.7, -17.2)	-23.3 (-24.2, -22.5)	-28.9 (-29.7, -28.1)	-34.6 (-35.4, -33.7)	-39.9 (-40.7, -39.1)	β = -5.85, SE = 0.154 P = $5.0*10^{-304}$
Black/African (N=788)		-22.4 (-23.3, -21.5)	-28.0 (-28.9, -27.2)	-33.7 (-34.6, -33.0)	-39.4 (-39.7, -38.8)	β = -5.74, SE = 0.726 P = $9.0*10^{-15}$
Hispanic/Latino (N=1,581)	-16.9 (-17.4, -16.0)	-22.4 (-23.5, -21.5)	-28.1 (-29.0, -27.2)	-33.7 (-34.6, -32.9)	-38.8 (-39.8, -38.0)	β = -6.41, SE = 0.541 P = $5.1*10^{-31}$
East Asian (N=1,435)	-17.5 (-18.0, -16.9)	-23.9 (-24.7, -23.0)	-29.5 (-30.4, -28.6)	-35.0 (-35.8, -34.2)	-41.0 (-41.7, -40.3)	β = -4.77, SE = 0.602 P = $4.7*10^{-15}$

Values are median percent reduction (interquartile range) of fitted values across defined daily dose (DDD) groups. SE, standard error.

Supplemental Table 3: Statin low-density lipoprotein cholesterol (LDL-C) dose-response by sex and race/ethnicity among simvastatin users

	1/8	1/4	1/2	1	2	4	Dose response
Male (N=4,716)	-21.1 (-21.1, -21.1)	-25.2 (-26.0, -24.3)	-30.8 (-31.5, -30.0)	-36.2 (-36.9, -35.4)	-41.8 (-42.6, -41.1)	-47.4 (-48.0, -46.6)	β = -5.35, SE = 0.342 P = $6.1*10^{-54}$
Female (N=5,736)	-19.3 (-20.2, -18.5)	-26.4 (-27.1, -25.7)	-31.8 (-32.6, -31.0)	-37.3 (-38.0, -36.5)	-42.7 (-43.5, -42.0)	-48.3 (-49.0, -47.6)	β = -5.54, SE = 0.265 P = $2.1*10^{-93}$
White/European (N=8.629)	-21.1 (-21.1, -21.1)	-26.0 (-26.9, -25.1)	-31.4 (-32.2, -30.6)	-36.8 (-37.7, -36.0)	-42.4 (-43.1, -41.6)	-47.9 (-48.7, -47.1)	β = -5.73, SE = 0.2228 P = $1.7*10^{-134}$
Black/African (N=315)		-25.4 (-25.9, -24.5)	-30.7 (-32.2, -29.3)	-36.0 (-36.7, -35.3)	-41.3 (-42.0, -40.7)	-47.8 (-48.3, -46.7)	β = -5.62, SE = 1.162 P = $2.1*10^{-6}$
Hispanic/Latino (N=831)	-17.6 (-17.6, -17.6)	-24.9 (-25.7, -24.2)	-30.6 (-31.2, -29.8)	-35.9 (-36.8, -35.0)	-41.6 (-42.3, -40.6)	-47.1 (-47.9, -46.4)	β = -4.32, SE = 0.782 P = $4.5*10^{-8}$
East Asian (N=677)		-26.7 (-27.7, -26.1)	-32.0 (-32.9, -31.3)	-37.3 (-38.2, -36.2)	-42.9 (-43.9, -42.0)	-48.3 (-49.0, -47.4)	β = -3.58, SE = 0.978 P = $2.7*10^{-4}$

Values are median percent reduction (interquartile range) of fitted values across defined daily dose (DDD) groups. SE, standard error.

Supplemental Table 4: Revised statin dose low-density lipoprotein cholesterol (LDL-C) lowering equivalency chart for the generation of defined daily dose (DDD) values

DDD	Daily dose (mg) *			
	Atorva	Lova	Prava	Simva
1/8			10	
1/4		10	20	
3/8				5
1/2		20	40	
3/4				10
1	10	40	80	
3/2				20
2	20	80		
3				40
4	40			
6				80
8	80			

*Daily dose equivalencies across type for each DDD value were based on statin-induced LDL-C changes among statin type observed in the present study population

Atorva, atorvastatin; lova, lovastatin; prava, pravastatin; simva, simvastatin

Supplemental Table 5. Predictors of low-density lipoprotein cholesterol (LDL-C) response to statin therapy (percent reduction) using revised defined daily dose (DDD) equivalencies

Covariate	Beta (SE)	P-value*
Log_2(DDD)	-5.58 (0.114)	$<10^{-300}$
Age†	-0.09 (0.010)	$5.9*10^{-21}$
Smoking	0.96 (0.185)	$2.5*10^{-7}$
Female	-0.89 (0.185)	$1.3*10^{-6}$
Diabetes	0.96 (0.244)	$8.3*10^{-5}$
Simvastatin‡	1.12 (0.288)	$9.8*10^{-5}$
Hypertension	-0.01 (0.197)	0.952
Pravastatin‡	-0.11 (0.711)	0.874
Black/African§	0.34 (0.503)	0.501
BMI	0.01 (0.019)	0.444
Hispanic/Latino§	0.41 (0.347)	0.237
Atorvastatin‡	-0.67 (0.529)	0.206
East Asian§	-0.83 (0.373)	0.027

*Multivariate linear regression

†Age at statin initiation

‡Lovastatin was set as the reference group

§White/European was set as the reference group

BMI, body mass index; SE, standard error.

Supplemental Table 6: Predictors of triglyceride (TG) response to statin therapy

Covariate	Beta (SE)	P-value[*]
Log_2(DDD)	-2.90 (0.241)	$2.0*10^{-33}$
Diabetes	-3.00 (0.514)	$5.1*10^{-9}$
Atorvastatin[†]	-3.54 (1.113)	0.001
East Asian[‡]	2.35 (0.783)	0.003
BMI	0.11 (0.040)	0.005
Simvastatin[†]	-1.03 (0.513)	0.045
Age[§]	-0.04 (0.021)	0.051
Smoking	0.40 (0.389)	0.305
Female	-0.29 (0.388)	0.460
Hypertension	-0.27 (0.414)	0.504
Pravastatin[†]	0.74 (1.485)	0.617
Black/African[‡]	-0.38 (1.057)	0.718
Hispanic/Latino[‡]	0.20 (0.729)	0.787

[*]Multivariate linear regression

[†]Lovastatin was set as the reference group

[‡]White/European was set as the reference group

[§]Age at statin initiation

BMI, body mass index; DDD, defined daily dose; SE, standard error.

Full multivariate model adjusted $R^2 = 0.011$

Supplemental Table 7: Predictors of high-density lipoprotein cholesterol (HDL-C) response to statin therapy

Covariate	Beta (SE)	P-value*
Black/African†	-1.90 (0.424)	$7.7*10^{-6}$
Simvastatin‡	0.90 (0.206)	$1.3*10^{-5}$
Female	-0.67 (0.156)	$1.6*10^{-5}$
Log_2(DDD)	-0.41 (0.097)	$2.4*10^{-5}$
Age§	-0.03 (0.008)	$1.1*10^{-4}$
Diabetes	0.63 (0.206)	0.002
Pravastatin‡	1.38 (0.595)	0.021
BMI	-0.03 (0.016)	0.094
Smoking	0.25 (0.156)	0.103
Atorvastatin‡	-0.53 (0.446)	0.237
Hypertension	-0.13 (0.166)	0.422
Hispanic/Latino†	-0.009 (0.292)	0.976
East Asian†	-0.004 (0.314)	0.989

*Multivariate linear regression

†White/European was set as the reference group

‡Lovastatin was set as the reference group

§Age at statin initiation

BMI, body mass index; DDD, defined daily dose; SE, standard error.

Full multivariate model adjusted $R^2 = 0.003$

Supplemental Table 8: Predictors of non-HDL-cholesterol (non-HDL-C) response to statin therapy

Covariate	Beta (SE)	P-value*
Log_2(DDD)	-5.27 (0.100)	$<10^{-300}$
Simvastatin†	-1.88 (0.213)	$1.3*10^{-18}$
Age‡	-0.07 (0.009)	$6.7*10^{-17}$
Pravastatin†	4.22 (0.618)	$8.3*10^{-12}$
BMI	0.10 (0.017)	$3.5*10^{-9}$
Smoking	0.86 (0.162)	$1.1*10^{-7}$
Female	-0.68 (0.161)	$2.6*10^{-5}$
Diabetes	0.60 (0.214)	0.005
Atorvastatin†	-1.13 (0.463)	0.015
Hispanic/Latino§	0.46 (0.303)	0.127
Hypertension	0.21 (0.172)	0.228
Black/African§	-0.33 (0.440)	0.448
East Asian§	-0.19 (0.326)	0.560

*Multivariate linear regression

†Lovastatin was set as the reference group

‡Age at statin initiation

§White/European was set as the reference group

BMI, body mass index; DDD, defined daily dose; SE, standard error.

Full multivariate model adjusted $R^2 = 0.151$

Supplemental Figure 1: Sample size of participants by statin type initiated across defined daily dose (DDD)

Supplemental Figure 2: Selection of lipid panels to calculate statin response

For a participant to be included in the study, he or she had to have ≥1 qualifying pretreatment and ≥1 qualifying on-treatment lipid panel. In addition, the earliest on-treatment lipid panel had to be within a window (dashed line) that started 20 days from initiation of statin treatment and ended 20 days after the completion of the statin days' supply. Only the most recent pretreatment and earliest on-treatment lipid panels (both denoted as blue circles) were used to calculate statin response.

Circles = dates of lipid panel. Squares = dispense dates of statin prescription. Blue rectangles = the full course of statin coverage from first day of a prescription to the end of days' supply.

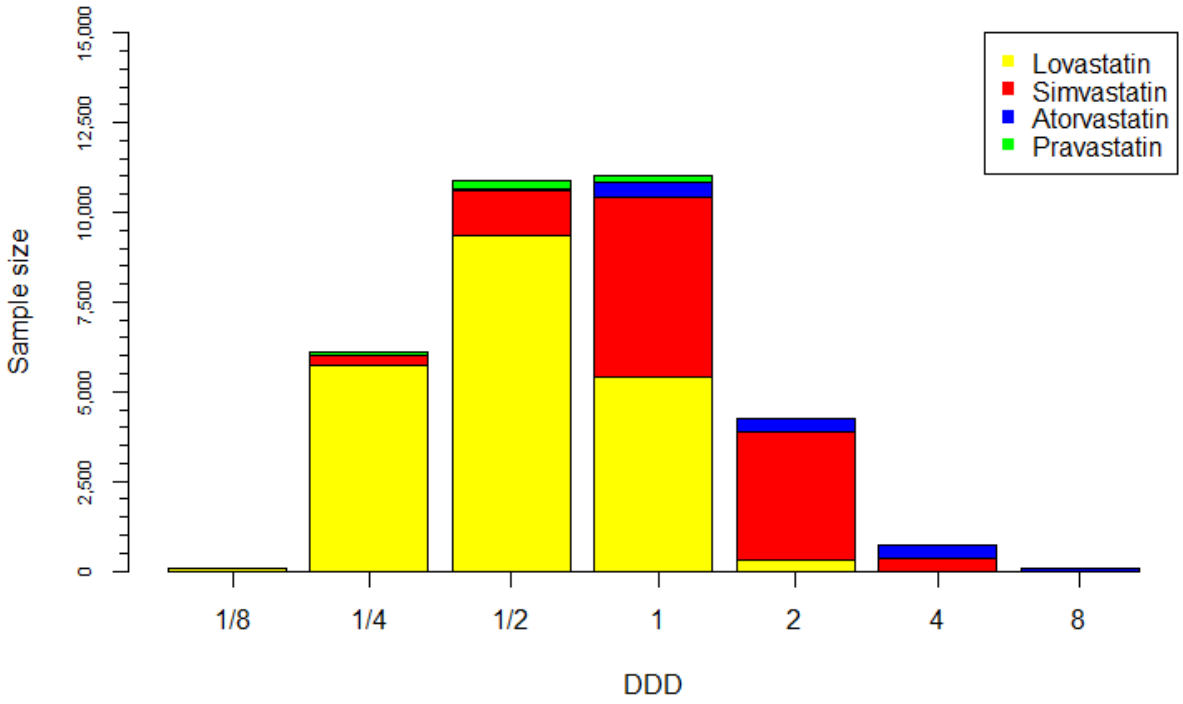
Supplemental Figure 3: Statin dose-response by race/ethnicity

A significant log-linear dose-response was observed in White/European (β = -5.10, SE = 0.129; $P < 10^{-300}$; N = 32,534), Black/African (β = -5.41, SE = 0.593, P = 2.6*10^-19; N = 1,374), East Asian (β = -4.01; SE = 0.473; $P = 3.9*10^{-17}$; N = 2,637), and Hispanic/Latino populations (β = -5.12; SE = 0.439; $P = 8.0*10^{-31}$, N = 3,206) after adjusting for pre-specified covariates.

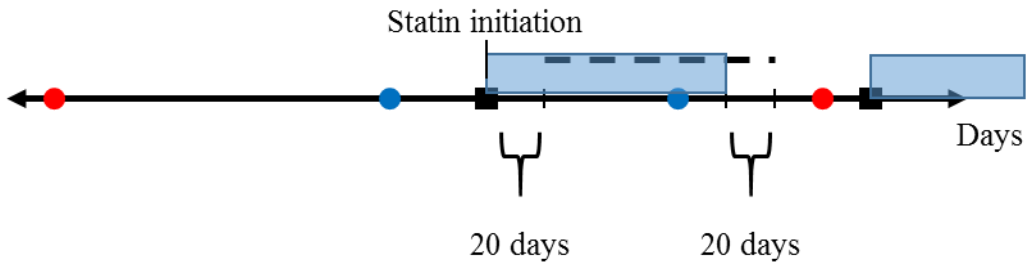
Data presented as the median (midline), interquartile range (box), and Tukey whiskers (dotted lines) of fitted values. Outliers are not shown.

DDD, defined daily dose; LDL-C, low-density lipoprotein cholesterol; SE, standard error.

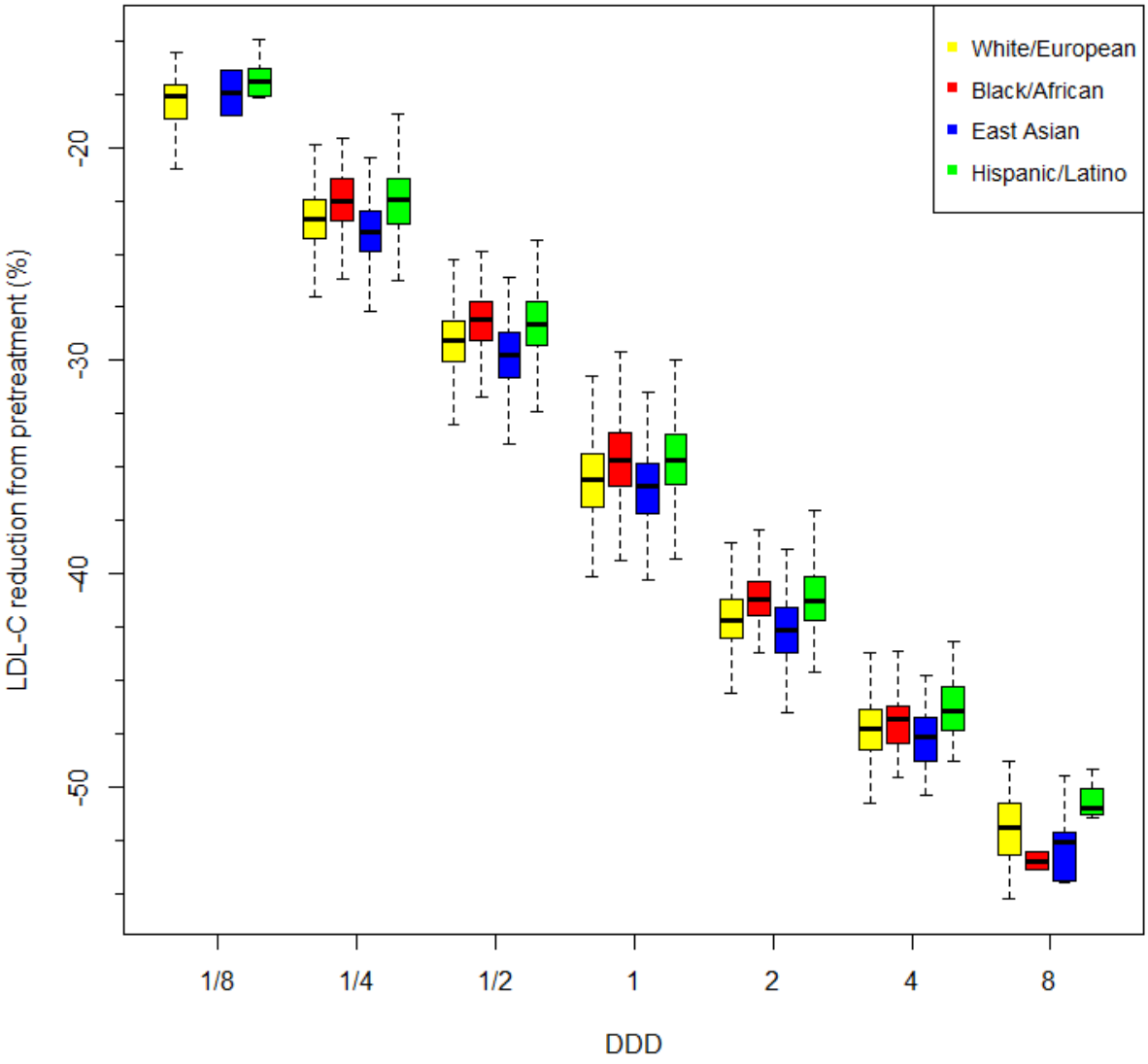
Supplemental Figure 1: Sample size of participants by statin type initiated across defined daily dose (DDD)



Supplemental Figure 2: Selection of lipid panels to calculate statin response



Supplemental Figure 3: Statin dose-response by race/ethnicity



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